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Allergen immunotherapy as a drug: the new deal of grass allergen tablets from clinical trials to current practice

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SUMMARY

Currently, sublingual immunotherapy (SLIT) may be performed by a number of allergen extract in different preparations but in a near future only products fulfilling the requirements from the regulatory agencies, that make mandatory a pharmaceutical quality, will be authorized. Indeed, two products with such characteristics are already available for SLIT in grass pollen allergic patients, Grazax® from Alk-Abellò and Oralair® from Stallergenes. The data from registrative trials as well as from post-marketing studies provide evidence of efficacy and safety of such products. This articles reviews the similarities and the differences of Grazax® and Oralair®, both designed as drugs for the treatment of grass pollen allergy with the aim, which is exclusive of allergen immunotherapy, to work on the natural history of allergy and not only on symptoms as rescue medications do. The aim of this paper is to evaluate the available trials with Grazax® and Oralair® in terms of pre-seasonal schedule approach to support their use in clinical practice. Such kind of treatment makes possible a continuous dialogue between clinical investigators and clinical practitioners, and is the only way for scientific progress that puts the patient's health at the first place.

ABBREVIATIONS

SCIT: Sub-Cutaneous ImmunoTherapy; SLIT: Sub-Lingual ImmunoTherapy; NPPs: Name Patient Products; MA: Marketing Authorization; DBPCTs: Double Blind Placebo Controlled Trials; DBRCTs: Double Blind Randomised Controlled Trials; TCS: Total Combined Score of the daily symptom score and the daily medication score; DSS: Daily Symptom Score; DMS: Daily Medication Score; RTSS: Rhinoconjunctivitis Total Symptom Score; RMS: Rescue Medication Score; ARTSS: Average Rhinoconjunctivitis Total Symptom Score; ACC: Allergen Challenge Chamber; VCC: Vienna Challenge Chamber; AE: Adverse Event.

Introduction

In 1911 Leonard Noon "invented" allergen immunotherapy (AIT), using a grass pollen extract by the subcutaneous route (1). Today, one hundred years later, the treatment of allergic diseases, and particularly of respiratory allergy, is based on allergen avoidance and on drug treatment, including anti-histamines, corticosteroids, anti-leukotrienes, and others, to obtain a symptom relief, but only AIT is able to change the natural course of the allergic disease (2), thereby preventing its exacerbations, and the possible progression from rhinoconjunctivitis to asthma symptoms (3-5). These aspects are particularly important for children, in whom the possibility of altering the

natural course of the disease seems really feasible (6). To the original subcutaneous immunotherapy (SCIT), among a number of alternative routes of administration, sublingual immunotherapy (SLIT) was demonstrated as a true option, showing a comparable efficacy and a better safety than SCIT (7). A pivotal issue in SIT is the quality of allergen extracts, that must contain all the clinically relevant allergens and must be standardized.

New products for immunotherapy

Today, most immunotherapy preparations are still "Named Patient Products" (NPPs) (8), that is, individual products prepared according to the physician's prescription, which in turn is oriented by the results of allergy tests. This makes SIT hardly credible for the scientific community, especially when mixtures of unrelated allergens are used.
The exceptions are Grazax® (Alk-Abellò, Horsholm, Denmark) and Oralair® (Stallergenes, Antony, France), that are both SLIT products for grass pollen AIT which have fulfilled all the requirements and procedures to be licensed as drugs. Using these two products thus far a total of 7 large phase III trials have been carried out both in adults (4 trials) (9-12) and children (3 trials) (13-15), involving more than 2500 grass allergic patients.
Grazax® is available in the form of an oral lyophilisate (a freeze-dried tablet), which must be placed under the tongue, where it disperses. Each lyophilisate contains 75,000 standardized quality units of grass pollen from the timothy grass (Phleum pratense). In September 2009, Grazax® was approved as the first registered disease-modifying AIT preparation for grass pollen allergic rhinoconjunctivitis in adults and children (5 years and older) (16). The dose is the same for adults and children (one tablet daily), starting, directly with the maintenance dose, at least 4 months before the expected pollen season. The recommendation by Alk-Abellò is to continue treatment with Grazax® for a period of 3 years. In Germany, Grazax® has been available since November 2006, in the majority of European countries since 2007, and in Italy since February 2008.
Oralair® is a sublingual allergen immunotherapy tablet. The Oralair® active substance consists of a purified and calibrated pollen extract containing 300 index of reactivity (IR) of five grass pollen allergen extracts corresponding to the epidemiological characteristics of patient exposure: perennial ryegrass (*Lolium perenne*), meadow grass (*Poa*

pratensis), timothy grass (*Phleum pratense*), cocksfoot (*Dactylis glomerata*) and sweet vernal grass (*Anthoxanthum odoratum*).
In adults, adolescents and children above the age of 5 years, therapy with Oralair® is based on a short build-up phase, with a three day dose escalation, and a maintenance treatment. The initial treatment corresponds to the first month of administration of Oralair® and the maintenance treatment is given from the second month, based on one 300 IR sublingual tablet daily until the end of the pollen season.
It is recommended that the tablet is taken in the morning, on an empty stomach. The tablet is placed under the tongue until complete dissolution (for at least one minute) and then swallowed. Oralair® has been marketed in Europe since 2008 and is available in Italy since December 2010.

Comparing the two drugs

Often clinical allergists operate as pioneers in their work, because they prescribe therapy tested in clinical trials to patients living in real life, in presence of a complexity of variables that can modify the results obtained from well-conducted controlled clinical trials. In real life we have to face the patients' compliance, the costs of immunotherapy, and the restrictions in prescribing arising from local specific laws and regulations.
Grazax® was born as a continuous SLIT treatment to be taken every day for a duration of at least 3 years but, because a pre-seasonal schedule for grass immunotherapy has been available and accepted by the scientific community (16), many clinical allergists started prescribing Grazax® about 8 weeks before the pollen season and for all the duration of the pollen season, in order to adapt immunotherapy to patient's life needs.
Oralair® was born as pre-coseasonal immunotherapy for grass pollen to be taken every day starting at least 8 weeks for all the pollen season. From the Horak et al. study there is also evidence that Oralair® seems to be effective even if tablets assumption starts 4 weeks before the pollen season (17). The overall evaluation of the available literature on SLIT would suggest that a pre-coseasonal regimen, starting at least 8 weeks before the pollen season would be the best choice for pollen SLIT (18).
The aim of this paper is to evaluate the available trials with Grazax® and Oralair® in terms of pre-seasonal schedule approach to support their use in clinical practice.

Methods

Data source

Medical literature information published in English between 1 January 1990 and 20 January 2012 was identified using MEDLINE/PubMed, EMBASE, SCOPUS, and The Cochrane Library; references were also required to ALK Abellò and Stallergenes.

Search Strategy

MEDLINE/PubMed, EMBASE, SCOPUS, and The Cochrane Library search terms (variously combined) were: Desensitization, Immunotherapy, tablets, grass pollen, Grazax, Oralair, patients, AIT.
Searches (last updated 20 January 2012) provided 37 articles, excluding duplicates.

Data Selection

Selected on the basis of their full-text article, reporting primary data about clinical phase III trials on use of grass pollen immunotherapy with AIT products.
To make sure to consider all the phase III trials presented for Marketing Authorization procedures by Alk-Abellò and Stallergenes, we asked both Companies to send us a summary of those studies.
We excluded studies based on the same initial cohort of patients (like follow up of sub groups of patients in the years) and we considered a total of 4 studies for Grazax® (Alk-Abellò) and 3 studies for Oralair® (Stallergenes).
The authors were the only reviewers who performed selection and data extraction.

Results

The grass tablets pre-seasonal schedule use, clinical trials and real life

Grazax® has been shown to be effective and safe in four phase III Double Blind Placebo Controlled Trials (DBPCTs): 2 on European populations (9, 10) and 2 on North American populations (19, 20). These studies were carried out for a duration of 4 to 7 months (mean treatment duration 184 days or 6 months); the administration started 16 weeks before the expected start of the grass pollen season (8 weeks in Bufe's trial (13)). These trials

have involved more than 1500 grass allergic patients (Table 1).
The first trial, from Dahl et al, was the GT-08 (8). In this trial, 634 European adult patients (mean age 34 years) with grass pollen-induced rhinoconjunctivitis were randomised at the beginning to Grazax® or placebo, to be taken daily. Treatment was started at least 16 weeks before the expected start of the grass pollen season, and planned to continue for 3 years, followed by 2 years' follow-up. The stated primary outcome was the mean daily rhinoconjunctivitis symptom score (DSS) during the first grass pollen season (a maximum score of 18 based on six rhinoconjunctivitis symptoms, scored 0 [no symptoms] to 3 [severe symptoms]). A total of 546 patients completed the first year of the study. The primary outcome was lower with Grazax® (2.4 vs. 3.4 with placebo, $p<0.0001$). Another outcome measure was the daily relief medication score (DMS) (6 points per desloratadine 5mg, 1 point per 4μg puff of budesonide nasal spray, 1.6 points per prednisone 5mg) for which there was a mean score of 1.5 with Grazax® vs. 2.4 with placebo ($p<0.0001$). In particular after 7 months therapy a 30% DSS reduction and 38% DMS reduction was observed with Grazax® during the first grass pollen season.
Another relevant trial was Bufe's et al. (GT-12 study) (13), that was carried out on European children (aged 5–16 years) as a double-blind randomized controlled trial (DBRCT). GT-12 involved 253 children (with or without mild–moderate asthma) who had a history of grass-pollen-induced allergic rhinoconjunctivitis. They were allocated to receive Grazax® or placebo, daily, starting at least 8 weeks before the start of the grass pollen season and continuing throughout the season. The rhinoconjunctivitis symptom score (a maximum of 18 points) was a primary outcome measure, as was the asthma score (a maximum of 12 points). Among the 234 (92%) children who completed the trial, mean rhinoconjunctivitis score during the entire grass pollen season was less with Grazax® (2.67 vs. 3.17 with placebo, $p=0.02$). At the first pollen season, after 6.6 months, the therapy reductions in DSS and DMS were 24% and 34% respectively. Furthermore, it was observed an increase in the level of grass allergen–specific IgG4 antibodies for the active group; this increase was consistent with the observed increase in the IgE-blocking factor, which assesses the effect of treatment-induced serum components competing with IgE for binding to the allergen.
Nelson et al. carried out a study in North America involving 439 adults with grass pollen− induced allergic rhinoconjuctivitis with or without asthma that were ran-

Table 1 - Synopsis of Phase III Grazax® studies

Trial (First Author, year, reference number)	No. of pts	Type of pts / Type of the disease of pts included in the study	Administration schedule (months before pollen season pollen season and throughout the pollen season)	Treatment duration in days	DSS reduction	DMS reduction
Dahl et al. ,2006 (9)	634	Adults / Grass pollen-induced rhinoconjuctivitis	4	210 (7 months)	-30%	-38%
Bufe et al.,2009 (13)	253	Children- adolescents/ Grass pollen-induced rhinoconjuctivitis with/without asthma	2-4	200 (6.6 months)	-24%	-34%
Nelson et al., 2011 (19)	439	Adults / Grass pollen-induced rhinoconjuctivitis with/without asthma	4	161 (5.3 months)	-18%	-26%
Blaiss et al.,2011 (20)	245	Children − adolescents / Grass pollen-induced rhinoconjuctivitis with/without asthma	4	168 (5.3 months)	-25%	-81%
Total	1571		2-4	184 (6 months)	-25%	-44%

domized to Grazax® once daily or placebo approximately 16 weeks before the 2009 grass pollen season (GPS) (19). The primary end point was the average total combined score of the daily symptom score and the daily medication score (TCS) during the grass pollen season. Compared with placebo, grass allergen tablet treatment improved TCS by 20% (P 5 .005), and DSS by 18% (P 5 .02). DMS were improved by 26% with a trend towards significance (P 5 .08) after 5.3 months of treatment. Furthermore, Phl p 5–specific IgG4 and IgE-blocking factor levels were higher after grass AIT treatment compared with those after placebo at the end of the GPS (P < .001).

Blaiss et al. carried out a trial in North American children and adolescents with grass pollen-induced rhinoconjuctivitis with or without asthma; 345 subjects (5-17 years old) were randomized to once-daily grass AIT treatment or placebo approximately 16 weeks before the 2009 GPS (20). The primary end point was the total combined score (TCS) of the daily symptom score (DSS) and daily medication score (DMS) for the entire GPS. TCS, DSS and DMS, score versus placebo improved 26% (P <

0.001), 25% (P <0.005), 81% (P = 0.006). Phl p5–specific IgG4 and IgE-blocking factor levels were significantly higher at the peak and end of the GPS (P <.001).

In all the mentioned trials, the adverse events (AE) were generally mild and transient. Review of all these data indicates that the use of Grazax® immunotherapy, started about 2-4 months before pollen peak and continued for few months during the pollen season, seems to be sufficiently effective and safe (16). However, it seems not advisable to use Grazax®, that starts directly with the maintenance dose, in subjects with an history of systemic reactions to SCIT, because anaphylactic reactions at the first dose were reported in such subjects (21).

Oralair® has been shown to be effective and safe in two phase III Double Blind Placebo Controlled Trials (DBPCTs): 1 with 628 adults and 1 with 253 children during pollen season, and in a study with 89 patients based on pollen chamber exposure: in total 1095 allergic patients have been involved in these trials (Table 2) (11,14). These studies have been carried out for a duration of 4 to 7 months.

Table 2 - Synopsis of Phase III Oralair® studies

Synopsis of Phase III Oralair® studies

Trial (First Author, year, reference number)	No. of pts	Type of pts / Type of the disease of pts included in the study	Administration schedule (months before pollen season pollen season and throughout the pollen season)	Treatment duration in days	RTSS reduction	RMS reduction
Didier et al., 2007 (11)	628	Adults / Grass pollen-induced rhinoconjuctivitis	4	162 (5.3 months)	-37%	-46%
Wahn et al., 2009 (14)	278	Children / Grass pollen-induced rhinoconjuctivitis	4	165 (5.3 months)	-39.3%	-48,7%
Total	906		4			

Oralair® study in Pollen Chamber

Trial (First Author, year, reference number)	N of pts	Type of pts / Type of the disease of pts included in the study	Decrease % ARTTS after 1 month	Decrease % ARTTS after 2 month	Decrease % ARTTS after 4 month	Oralair® improvement vs Placebo
Horak et al, 2009 (17)	89	Adults / moderate to severe seasonal grass pollen-allergic rhinoconjunctivitis	-5.89 (± 2431) P=0.0042	-5.09 ± 2.088 P=0.2003	-4.85 ± 1.995 P=0.0007	21.97%

The trial from Didier et al. (V034.04) involved 628 European patients with moderate-to-severe seasonal grass pollen–related allergic rhinoconjunctivitis (11). Approximately 5 months before the expected start of the pollen season, patients were screened for eligibility and randomized 1:1:1:1 to 1 of the 4 treatment groups (100 IR, 300 IR, 500 IR, or placebo) by using a computer-generated randomization list. The first dose was administered 4 months before the expected start of the grass pollen season. No differences were observed for the baseline characteristics in the 4 treatment groups; the mean treatment duration before the pollen season was similar in all groups.

Rhinoconjunctivitis symptoms were lower in the 300-IR and 500-IR groups during the pollen season than in the 100-IR and placebo groups. Compared with placebo, median RTSS in the 300-IR group demonstrated 37% improvement, whereas patients taking 500 IR had 35% improvement. The proportions of days with rescue medica-

tion usage (RMS) were lower in the 300-IR and 500-IR groups than in the 100-IR and the placebo groups. Patients in the 300-IR group reported significantly less rescue medication use (46%) compared with those taking placebo.

During the study, grass-specific IgG4 (mg/L) levels increased 2.7-fold in the 100-IR group, 3.2-fold in the 300-IR group, and 3.7- fold in the 500-IR group compared with the placebo group. The progressive mean IgG4 level elevations. corresponded with increasing SLIT dose, which suggests a dose-effect for IgG4.

The IgE (kU/L) levels increased by a factor of 2.0 for the 100-IR group, 2.1 for the 300-IR, group and 2.2 for the 500-IR group, whereas for the placebo group, the geometric means were remained constant at the 2 visits (a ratio of 1.0).

The trial from Wahn et al. (V052.06) was a European, multinational, double-blind, placebo-controlled, phase III study in children with grass pollen–related allergic rhinitis

and included 278 children and adolescents with seasonal grass pollen–related allergic rhinitis (14). After screening, eligible patients were randomized 1:1 to 2 groups: one group received once-daily SLIT with 300 IR of allergen extract in a tablet formulation, and the other group received placebo. All characteristics were well balanced at baseline between treatment groups. The primary outcome was the efficacy of the treatment on the rhinoconjunctivitis total symptom score (RTSS), which included the 6 most common symptoms of pollinosis (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes). A score ranging from 0 to 3 was used for each symptom: 0, no symptoms; 1 mild, 2 moderate and 3, severe symptoms. In case of severe symptoms, patients could use rescue medication. The daily rescue medication score (0, no medication; 1, antihistamine; 2, intranasal corticosteroid; 3, oral corticosteroid), and the proportion of days with rescue medication is Rescue Medicaton Score (RMS).

The mean RTSS during the pollen period in the 300-IR group was lower than that in the placebo group. Compared with the placebo group, the 300-IR group showed a mean improvement of 28.0% and a median improvement of 39.3% for the mean RTSS (Table 2).

The mean rescue medication score (RMS) of the 300-IR group was highly statistically significantly different from that of the placebo group. Compared with the placebo group, the 300-IR group showed a mean improvement of 24.1% and a median improvement of 48.7% for the mean rescue medication score (Table 2).

For children receiving the 300-IR dose, the geometric mean level of grass-specific IgG4 increased more than 3-fold from baseline (before treatment) to the end of treatment (ratio, 3.37), whereas children receiving placebo showed little change in IgG4 levels (ratio, 1.41).

By contrast, for timothy grass–specific IgE, the geometric mean level before treatment and at the end of treatment were similar for both those children who received active treatment (ratio, 1.35) and those who received placebo (ratio, 1.64).

The trial from Horak et al. (V056.07A), was a Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Single-Center Trial performed between the 2007 and 2008 grass pollen seasons, involving 89 patients aged between 18 and 50 years with a documented history of moderate-to-severe seasonal grass pollen–related allergic rhinoconjunctivitis (17). After an initial screening visit and a baseline allergen challenge, eligible patients were randomized 1:1 to receive either a 300-IR SLIT tablet or placebo. Patients underwent an allergen challenge in the chamber with grass pollen before treatment (the baseline challenge). Additional challenges were performed after 1 week and 1, 2, and 4 months of treatment (each lasting 4 hours). Treatment was taken daily at the dose of 300 IR from day 1 and for 4 months. Anti-histamines, decongestants, anti-leukotrienes, cromones, corticosteroids, and topical nasal or ocular treatments were prohibited during the treatment period. There was no necessity for rescue medication because the trial was performed out of season. The allergen challenge was carried out in the validated Vienna Challenge Chamber (VCC) (22) at the Allergy Center of Vienna, Austria.

During the challenge the patients scored the 6 individual rhinitis and conjunctivitis symptoms every 15 minutes on computer keypads. Nasal airflow was measured every 30 minutes by means of active anterior rhinomanometry. Nasal secretion was determined every 30 minutes by collecting and weighing used tissues; patients were given preweighed packs of paper tissues, which they used to blow their noses as necessary. FEV1 was measured every hour by using standard spirometric procedures. Initial measurements (except nasal secretion weight) were performed before patients entered the chamber. Blood was taken before treatment initiation and after 2 and 4 months of treatment. The RTSS includes the 6 most common symptoms of allergic rhinoconjunctivitis: sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and tearing. Each symptom was evaluated by the patient with a score ranging from 0 to 3, as follows: 0 absent symptoms; 1 mild, 2 moderate and 3 severe symptom. The RTSS is the sum of the 6 individual symptom scores and thus varies from 0 to 18. The RTSS was recorded every 15 minutes during the 4-hour allergen exposure challenge (2 hours at baseline). The average rhinoconjunctivitis total symptom score (ARTSS) for each patient was calculated for each challenge as he average of the RTSSs across the challenge's 16 time points (8 time points for baseline challenge).

The primary efficacy variable was the ARTSS during the allergen challenge after 4 months of treatment or at end point. In the course of the baseline challenge, individuals started free of symptoms and reached the worst symptoms after 90 to 120 minutes. Both groups reacted to the same amount. The 300-IR group had a significantly lower ARTSS during allergen challenge after 4 months of treatment (or at end point) than the placebo group (21.97%). For the 300-IR group, a significant treatment effect was achieved after the first month (P .0042) and maintained

at 2 (P .0203) and 4 (P .0007) months. In the active group the ARTSS decreased at each challenge (5.89 2.431 at month 1, 5.09 2.088 at month 2, and 4.85 1.995 at month 4), whereas the lowest mean ARTSS was observed at month 2 in the placebo group (6.21 2.939). In the first year after treatment initiation, the specific IgE(kU/L) levels increased by a factor of 2.0 or more for all treatment groups, while for the placebo group, the geometric means remained similar at the two visits (a ratio of 1.0). Timothy grass IgG4 (mg/L) levels remained static in the placebo group but increased in all treatment groups. These increases in IgE and IgG4 levels (measured at the end of the first pollen season) were highly significant in all treatment groups, compared with placebo (P < 0.0001).

It is noteworthy that the phase III studies carried out with both Grazax® and Oralair® indicated for grass induced rhinoconjuctivitis adopted the same therapeutic duration approach (4 month before the start the pollen season and throughout the entire season), with the exception for Bufe's trial (8 weeks) with Grazax® (13) and Horak's trial with Oralair® that demonstrates efficacy after 4 weeks treatment (17).

Discussion

The pre-seasonal schedules for pollen immunotherapy are generally well accepted in terms of costs and compliance: the patient is well disposed to accept a pre-seasonal tablet assumption but tends to forget to take immunotherapy when seasonal symptoms improve and the pollen season stops. Moreover, in some part of Italy (such as the Northern region Lombardia), patients may receive immunotherapy by total reimbursement only if prescribed for 4 months. These issues make the pre-seasonal schedule the most suitable schedule for pollens in clinical practice instead of continuous immunotherapy.

The number of subjects treated with Grazax® in the mentioned trials is consistent (1619 patients). The overall results obtained in these studies support the contention that reductions in rhino-conjunctivitis medication and symptoms score translate into important benefits for the subjects and therefore can be considered clinically relevant (23). Furthermore, another trial showed that treatment with Grazax® induced a time-dependent increase in allergen specific IgE, IgG and IgA antibody responses during the preseasonal treatment period (8 weeks) (24). This suggests that the treatment had a significant effect on the immune system in an allergen specific manner, and that the duration of preseasonal treatment potentially could influence the clinical efficacy (25).

Although no proper pre-seasonal trials with Grazax® are today available, we can be optimistic about the pre-seasonal use of this product because it seems to give worthwhile results since the first months of the first year of treatment, in adult, in children and adolescents, according to patient's compliance but more evidence is required.

After its restart, in which the continuous use was suggested from the randomized controlled trials, Grazax® must now grow up and move to new horizons.

By contrast, Oralair® was specifically designed to be a precoseasonal treatment and good evidence in this regard was provided from clinical trials (26). Oralair® is now approaching the full clinical practice in Italy and surely more data will be available from use in real life in the next grass pollen seasons. Another question to answer in clinical practice is whether a preparation with one grass pollen extract (Grazax®) or one with 5 grass pollens extract (Oralair®) is better for treating patients in real life. Both therapeutic strategy have been supported by relevant scientific data, but it is apparent that the distribution of grasses in the different geographical areas is a critical factor. In fact, an extract with only Phleum pratense seems adequate for patients living in Northern Europe but not for patients living in Mediterranean areas. This is true for Italy, where phenologic studies demonstrated that there are relevant differences in effective flowering of the grass species. In fact, only some species contributed to the pollen peak, and a significant pollen load for other species was present out of the seasonal peak. Important grasses, such as timothy grass, were not present during the pollen peak in northern and central Italy, and the same occurred with Bermuda grass (27).

Another important point is that epidemiologic and clinical trial data show that 51% to 81% of US and European patients are polysensitized. In Europe most allergen AIT formulations are single-allergen extracts (even for polysensitized patients), whereas preparations in the US contain an average of 8 different components. In two recent post hoc analysis of two DBPC studies conducted respectively with once-daily sublingual tablets containing extracts of 5 related grass pollens at doses of 100, 300, or 500 IR or placebo and with once-daily sublingual tablets containing *Phleum pratense* pollen extract at a dose of 75,000 SQ-T/2,800 bioequivalent allergen units or placebo, it was demonstrated that single-allergen immunotherapy was safe and effective in polysensitized patients as in monosensitized patients (12,28,29).

In conclusion, today we have two proper drugs for grass pollen immunotherapy with regular marketing authorization: Grazax® (*Pleum pratense extract*), initially designed for continuous immunotherapy, that was subsequently successfully used in clinical practice also with pre-seasonal schedule, and Oralair® (mix of five grass pollens extracts) born as pre-seasonal drug and currently successfully used in clinical practice. Which patient for which grass pollen drug? We have no definite answer today. Probably the answer could come from clinical observation of patients in real life and in the future maybe we could consider the grass pollen patient phenotype as we are starting to do for some subsets of patients with asthma (30). A continuous dialogue between clinical investigators and clinical practitioners is the only way for scientific progress that puts the patient's health at the first place.

Disclosure of interest

Acnowledgements

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